

Cardiac hemodynamics and proinflammatory cytokines during biatrial and right atrial appendage pacing in patients with interatrial block

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Abstract

Purpose Interatrial block (IAB) frequently coexists with sinus node disease and is considered a risk factor of left atrial dysfunction, atrial arrhythmias, and heart failure development. Conventional right atrial appendage (RAA) pacing impairs intra- and interatrial conductions and consequently prolongs P wave duration. Biatrial (BiA) pacing helps correct IAB, but its advantageous influence remains controversial. The aim of the study was to compare the effects of BiA and RAA pacing on cardiac hemodynamics and serum concentrations of inflammatory markers and neuropeptides.

Methods Twenty-eight patients with IAB and preserved atrio-ventricular conduction treated with BiA pacing were studied. Standard invasive hemodynamic measurements were performed during BiA and RAA pacings. Furthermore, the influence of 1 week of BiA and RAA pacing on neuropeptides: atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) and markers of inflammation: high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), and neopterin was examined.

Results BiA pacing resulted in significant increase of cardiac output (CO) and reduction of pulmonary capillary wedge pressure. We demonstrated significantly lower concentrations of ANP, hs-CRP, IL-6, and neopterin after 1 week of

BiA in comparison to RAA pacing. BNP levels remained unchanged.

Conclusions BiA pacing in comparison to RAA pacing improves hemodynamic performance in patients with IAB and preserved atrio-ventricular conduction. BiA pacing is associated with reduction of ANP and markers of inflammation (hs-CRP, IL-6, and neopterin).

Keywords Biatrial pacing · Cardiac hemodynamics · ANP · hs-CRP · IL-6 · Neopterin

1 Background

Interatrial block (IAB) is defined as impaired conduction between right and left atrium (LA) and is reflected by prolonged P wave duration exceeding 120 ms on the surface ECG. IAB can be identified in up to 40–50 % of routinely performed ECGs but is frequently overlooked or ignored [1, 2]. IAB is associated with atrial electromechanical dysfunction, which in conjunction with delayed LA contraction in relation to left ventricular (LV) contraction, may reduce cardiac output [3, 4]. In patients with atrio-ventricular (A-V) block, IAB might be partially balanced, restoring the timing in the left heart. However, IAB does not always coexist with A-V conduction prolongation.

Right atrial appendage (RAA) is still the conventional location of atrial lead. Nonetheless, it has been demonstrated that RAA pacing may induce or exacerbate intra- and interatrial conduction disturbances [5, 6]. Biatrial (BiA) pacing is one of the methods of reducing IAB and decreasing the incidence of atrial tachyarrhythmias [7–9]. With respect to cardiac hemodynamics, however, the superiority

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of BiA over standard RAA pacing remains controversial as data from available studies are conflicting [10–14].

The aim of the present study was two-fold. Firstly, we aimed to investigate whether patients with IAB and intact A-V conduction (i.e., patients without the balancing effect of prolonged A-V conduction) could benefit from BiA in comparison to RAA pacing in terms of hemodynamic performance. Secondly, we aimed to determine the influence of both pacing modes on prognostic markers: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), and neopterin.

2 Material and methods

The study was conducted in patients with BiA pacemakers implanted as a standard practice in our center in the course of 1 year due to sinus node dysfunction, documented symptomatic recurrent atrial fibrillation (AF), signs of advanced intra- and interatrial conduction delay, and with indications for routine coronary angiography according to current European Society of Cardiology guidelines. Inclusion criteria were defined as follows: P-wave duration ≥ 120 ms during sinus rhythm, preserved A-V conduction (PQ interval ≤ 200 ms), and more than 85 % of pacing during 4 weeks before inclusion. Exclusion criteria included the following: structural heart disease, AF requiring cardioversion within 4 weeks before and throughout the study, symptomatic heart failure (HF) New York Heart Association (NYHA) class III or higher, active infections, history of malignancies and connective tissue diseases, anti-inflammatory/immunosuppressive treatment, and acute coronary syndrome within 3 months before enrolment. All patients with any AF episode during the hemodynamic assessment were excluded from the study. Patients were excluded from the biochemical part of the study if AF lasted longer than 24 h or required cardioversion.

Initially, 34 patients fulfilled inclusion criteria, 6 of whom were excluded from analysis due to infection (1) and AF recurrences (5). The study protocol was approved by the Ethics Committee of The Medical University of Lublin, Poland and followed the guidelines of the Declaration of Helsinki. Each participant gave written informed consent accepting the study protocol (Fig. 1).

2.1 Pacemaker implantation

All patients had BiA pacing system utilizing standard dual chamber pacemaker (Axios DR or Philos DR, Biotronik GmbH, Germany) implanted at least 6 weeks (6 to 45 weeks, median 8 weeks) before enrolment. Atrial channel was connected to the lead positioned in RAA and ventricular channel to the lead implanted in mid/distal coronary sinus

(CS) (Corox LA-H, Biotronik GmbH, Germany, bipolar, passive fixation). During BiA pacing, an A-V delay was set to 15 ms. In order to ensure stable atrial pacing, the basic rate was programmed at least 10 bpm above intrinsic sinus rate (AAI mode) to keep baseline heart rate 60–75 bpm (depending on baseline bradycardia) and was constant throughout the study. In each patient, 100 % pacing was ensured during echocardiographic and hemodynamic studies and at least 85 % during biochemical study. At the beginning of the study and each time the pacemaker was reprogrammed, the RAA and CS thresholds were checked, and the pacing impulse amplitude was programmed at least twice the measured pacing threshold. ECG tracings were printed after each reprogramming to confirm pacing mode and capture. Investigators who performed hemodynamic and echocardiographic measurements and laboratory tests were blinded to the pacing mode.

2.2 Hemodynamic study

Standard invasive hemodynamic measurements were obtained in fasting patients in supine position following routine coronary angiography. Measurements were recorded after at least 5-min randomly assigned pacing mode—RAA or BiA. Then, the pacing mode was switched to the other one (RAA or BiA), and after at least 5 min, measurements were repeated. Mid-chest position was used for the zero reference level. Cardiac output was determined by Fick method. Pressure curves were analyzed by two independent investigators.

2.3 Echocardiography

Echocardiography was performed following the joint guidelines of the European Association of Echocardiography and the American Society of Echocardiography using commercially available ultrasound system (iE33, Philips). LA volume was measured from standard apical two- and four-chamber views at end-systole. LA borders were traced using planimetry. LA volume index (LAVI) was calculated by dividing the LA volume by body surface area [15]. The closure of the mitral valve was determined from the parasternal long view using M-mode and timed to the QRS complex.

2.4 Biochemical study

Two weeks after hemodynamic measurements, the second part of the study was conducted in the same population. ANP, BNP, hs-CRP, IL-6, and neopterin were assayed twice: after 7 days of BiA and 7 days of RAA pacing in randomly assigned order (cross-over design). Blood samples were collected in fasting patients after at least 30 min of rest in supine position. Blood samples taken for cytokine analysis were immediately centrifuged (4,000 rpm for 10 min at 4 °C).

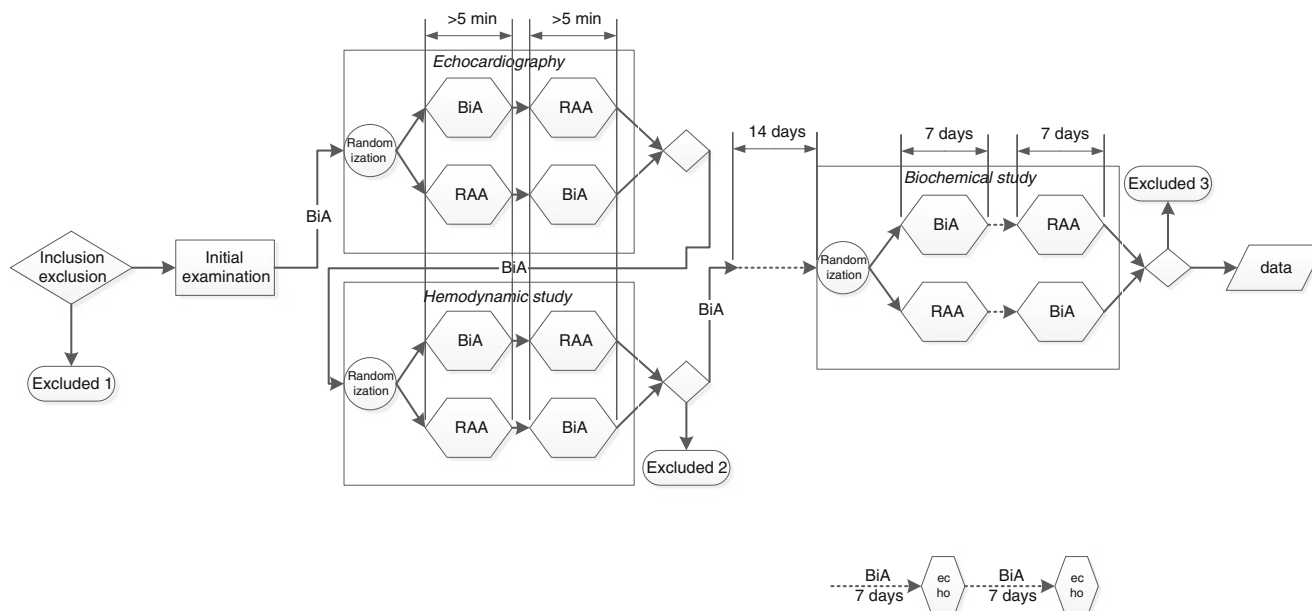


Fig. 1 Study protocol

Serum was frozen and kept at -80°C until assay. Concentrations of hs-CRP (IBL, USA), IL-6 (R&D, UK), and neopterin (R&D, UK) were determined with commercially available ELISA test kits in accordance with manufacturers' recommendations. Samples for ANP and BNP measurements were collected into ice-chilled tubes containing EDTA and aprotinin, centrifuged (2,000 rpm for 20 min at 4°C), frozen, and stored at -80°C until assay. ANP and BNP were assayed with commercially available ELISA test kits (BNP: IBL, Germany; ANP: Wuhan EIAab Science Co., Ltd). Additionally, basic blood tests were performed. All medications were kept constant throughout the study.

2.5 Statistical analysis

Data are presented as mean \pm standard deviation. Differences between measurements were compared with Wilcoxon's non-parametric test. A p value <0.05 was considered statistically significant.

3 Results

Initially, 34 patients fulfilled the inclusion criteria, 6 of whom were excluded from analysis due to infection (1) and AF recurrences (5). Two patients developed AF during the hemodynamic examination and 3 during the biochemical part of the study. All AF episodes occurred during RAA pacing. Consequently, 28 patients were analyzed (15 males, 13 females; mean age 66.6 years).

Baseline characteristics of the study population are summarized in Table 1. Results of ECG and echocardiographic

and invasive hemodynamic measurements are presented in Table 2. BiA pacing, in comparison to RAA pacing, resulted in statistically significant shortening of P wave duration (115 ± 11 vs. 173 ± 15 ms; $p=0.0001$) and PQ interval (190 ± 10 vs. 221 ± 14 ms; $p=0.0002$).

There were pronounced differences in the transmitral flow assessed by PW Doppler between the two pacing modes. Intervals from atrial pacing spike on the ECG to the onset (P-A onset), peak (P-A peak), and end (P-A end), of the mitral atrial filling wave (A) were significantly shorter during BiA in comparison to RAA pacing (87 ± 11 vs. 119 ± 15 ms, $p=0.0001$; 146 ± 11 vs. 190 ± 17 ms, $p=0.0001$; 214 ± 16 vs. 276 ± 15 ms, $p=0.0001$). Mitral inflow velocity time integral (VTI) (12.1 ± 2.1 vs. 9.9 ± 2.0 cm; $p=0.01$) and peak velocity of the mitral atrial wave (AVmax) (107 ± 10 vs. 90 ± 11 cm/s; $p=0.04$) were higher during BiA pacing.

Intervals between the end of the atrial filling wave of transmitral flow and the mitral valve closure (A end-MC) were significantly longer during BiA in comparison to RAA pacing (71 ± 32 vs. 36 ± 55 ms; $p=0.001$). In invasive hemodynamic examination, we observed beneficial effects of BiA in comparison to RAA pacing on cardiac hemodynamics. BiA pacing resulted in higher cardiac output (CO) (4.9 ± 0.8 vs. 4.1 ± 0.7 l/min; $p=0.02$) and lower pulmonary artery wedge pressure (PCWP) (11.0 ± 1.9 vs. 12.9 ± 2.1 mmHg; $p=0.02$).

In biochemical study, we demonstrated significantly lower serum concentrations of ANP, hs-CRP, IL-6, and neopterin after 1 week of BiA in comparison to RAA pacing. Concentrations of BNP remained unchanged. There were no differences in total blood count, serum urea, creatinine and glomerular filtration rate between both pacing modes.

Table 1 Patient characteristics ($n=28$)

	Number
With coronary artery disease	28
With hypertension	18
With heart failure class	
NYHA I	19
NYHA II	7
With diabetes	8
Mean left ventricular diastolic dimension (cm)	4.7±0.5
Mean right ventricular dimension (cm)	2.7±0.3
Mean ejection fraction (%)	57±4
Mean left atrial diameter (cm)	4.4±0.4
Mean P wave duration during sinus rhythm in lead II (ms)	145±13
Mean PQ interval during sinus rhythm in lead II (ms)	185±15
Mean QRS duration (ms)	92±12
Pharmacotherapy (%)	
ACEi	64
ARB	21
Beta-blocker	72
Propafenone	43
Amiodarone	14
Loop diuretic	28
VKA	72
ASA	75

ACEi angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, ASA acetylsalicylic acid, VKA vitamin K antagonist

4 Discussion

RAA is the standard lead position routinely used for permanent atrial pacing even in patients with coexisting interatrial conduction abnormalities. It has been demonstrated that RAA pacing exacerbates interatrial conduction disturbances and has unfavorable proarrhythmic and hemodynamic consequences [6]. However, it is still a matter of debate whether BiA in comparison to standard RAA pacing could improve hemodynamics and prognosis in individuals with IAB.

In our study, invasive hemodynamic measurements revealed CO increase and PCWP reduction during BiA in comparison to RAA pacing. Previous invasive hemodynamic studies indicating that BiA pacing might increase CO and decrease PCWP, when compared to high right atrium, concerned patients with IAB and dual chamber pacing (DDD) pacing [10, 12]. In order to elucidate the hemodynamic effect of pure BiA and RAA pacing and to avoid potential influence of A-V delay and ventricular pacing during DDD stimulation, we focused on patients with intact A-V conduction. Levy et al. [13] and Dabrowska-Kugacka et al. [11] did not find statistical differences in CO between RAA and BiA pacing. However, in both studies, echocardiography was used for LV systolic function evaluation, which obviously is less

accurate than invasive measurements. Furthermore, populations in both studies were small and consisted of only 8 and 14 patients, respectively. Furthermore, patients with prolonged A-V conduction and heart failure associated with interventricular conduction abnormalities were not excluded, which might have blunted the effect of BiA and RAA pacing on cardiac hemodynamics [16]. The population in the study of Levy et al. [13] consisted of patients with bradycardia-tachycardia syndrome, and the interatrial conduction was not specified. It has been already demonstrated that patients without baseline IAB do not benefit from BiA pacing compared to sinus rhythm, while RAA pacing has an unfavorable hemodynamic effect in this group [16].

In our study, echocardiographic examination revealed higher VTI of the mitral inflow as well as aortic VTI during BiA vs. RAA pacing, which confirms with the observations made by Matsumoto et al. [14]. It is known that BiA pacing improves atrial systolic function [16–19]. More synchronous LA segment contraction during BiA in comparison to single site (RAA or CS) pacing might explain this observation [17, 18]. A positive influence of BiA pacing on global systolic LA function was observed in the stunned atrium after cardioversion of persistent AF [20].

It has also been demonstrated that RAA pacing exacerbates interatrial conduction disturbances leading to unfavorable hemodynamic consequences [6]. RAA pacing was detrimental to cardiac electromechanical function when compared to sinus rhythm [20]. Since no measurements during sinus rhythm were performed in our study (because of substantial bradycardia), we cannot rule out the possibility that what we observed was not an advantageous effect of BiA but only a correction of an unfavorable effect of RAA pacing.

Analysis of mitral inflow during RAA pacing revealed that in the majority of our patients, there was no A end-MC delay, which suggested that LV contraction interrupted atrial filling. This effect was not observed during BiA pacing, which prolonged left heart A-V interval.

LV activation occurs earlier during BiA in comparison to RAA pacing, and consequently PQ interval is shortened. However, LA is also preactivated, which results in shorter P-A onset, P-A peak, and P-A end of the Doppler mitral A filling wave. This prevents mitral inflow restriction by premature mitral valve closure during BiA pacing.

The effects of change in left A-V timing (PQ duration, P-A intervals, duration of E and A waves, ventricular relaxation, and velocity of transmitral flow (peak mitral early filling velocity/EVmax and peak atrial filling velocity/AVmax)) should not be considered the independent benefits of BiA pacing because they are mutually dependent and are finally reflected in mitral and aortic VTI as well as CO. Improved CO during BiA, in comparison to RAA pacing, may be due to increased preload as a result of increased mitral inflow. LV relaxation begins as an initial diastolic process, and LV

Table 2 Effect of pacing site on cardiac hemodynamics, biochemical markers, and ECG parameters

Measurement/ marker/parameter	BiAp	RAAp	<i>p</i> value
Hemodynamic measurements			
RAP (mmHg)	5.6±2.3	6.0±2.1	ns
RV ESP (mmHg)	28.3±7.0	27.5±7.5	ns
RV EDP (mmHg)	7.4±2.5	7.8±2.8	ns
mPAP (mmHg)	18.1±4.4	17.9±4.3	ns
PCWP (mmHg)	11.0±1.9	12.9±2.1	0.02
mAP (mmHg)	106.3±12.5	104.4±12.7	ns
CO (l/min)	4.9±0.8	4.1±0.7	0.02
IVCP (mmHg)	6.5±3.5	7.1±4.1	ns
Echocardiographic measurements			
VTIm (cm)	12.1±2.1	9.9±2.0	0.01
EVmax (cm/s)	96±11	87±10	ns
AVmax (cm/s)	107±10	90±11	0.04
E/A ratio	0.89±0.12	0.88±0.12	ns
DTE (ms)	170±18	175±19	ns
IVRT (ms)	94±10	97±9	ns
LA area (cm ²)	24±5	24±6	ns
LAVI (ml/m ²)	41±5	42.5±5.5	ns
MR area (cm ²)	3.3±0.7	3.9±1.3	ns
P-A onset (ms)	87±11	119±15	0.0001
P-A peak (ms)	146±11	190±17	0.0001
P-A end (ms)	214±16	276±15	0.0001
A end-MC	71±32	36±55	0.001
AoVTI (cm)	34±5	30±8	0.02
AoPEP (ms)	108±18	105±17	ns
LVET (ms)	295±17	289±19	ns
Biochemical markers			
ANP (pg/ml)	199±45	265±48	0.002
BNP (pg/ml)	122±32	142±41	ns
hs-CRP (mg/ml)	2.1±0.4	2.8±0.5	0.02
Neopterin (pg/ml)	11.8±3.1	14.8±3.3	0.03
IL-6 (pg/ml)	4.4±0.6	5.3±0.7	0.02
Electrocardiographic parameters			
Paced P wave duration (ms)	115±11	173±15	0.0001
PQ interval (ms)	190±10	221±14	0.0002
QRS duration (ms)	91±12	92±11	ns
Mean pacing rate (bpm)	65±7	66±7	ns

Measurements during BiA and RAA pacings at a fixed rate were compared (*n*=28)

A end-MC interval between the end of the atrial filling wave of transmitral flow and the mitral valve closure, *ANP* atrial natriuretic peptide, *AoPEP* left ventricular pre-ejection time, *AoVTI* aortic velocity time integral, *AVmax* peak atrial filling velocity, *BNP* brain natriuretic peptide, *CO* cardiac output, *DTE* deceleration time of early filling velocity, *LVET* left ventricular ejection time, *EVmax* peak mitral early filling velocity, *hs-CRP* high sensitivity C-reactive protein, *IL-6* interleukin-6, *IVCP* inferior vena cava pressure, *IVRT* isovolumetric relaxation time, *LA* left atrial area, *LAVI* left atrial volume index, *mAP* mean arterial pressure, *mPAP* mean pulmonary artery pressure, *MR* mitral regurgitation area, *ns* not significant, *P-A* interval between the beginning of the atrial pacing spike and the onset/peak/end of mitral atrial filing wave, *PCWP* pulmonary capillary wedge pressure, *RAP* right atrial pressure, *RV ESP/EDP* right ventricular end-systolic/end-diastolic pressure, *VTIm* mitral velocity time integral

pressure falls rapidly as the LV expands. Myocardial relaxation continues during early diastole to reach the minimal LV diastolic pressure, which helps with “sucking” and “pulling” the blood actively into the LV. LV pressure then rises and the early diastolic filling decelerates until the time of atrial contraction when LA pressure increases again to initiate the late filling and to complete diastole. Mitral E inflow is sensitive to preload. It is becoming higher with shorter deceleration time (time from the peak to the baseline) as diastolic function deteriorates with increasing filling pressure [21]. Relaxation

abnormalities result in the reduction in the rate of LV pressure decline during the early diastole. Consequently, atrial contraction is responsible for a substantial proportion of diastolic filling. In our study, there was no difference in diastolic dysfunction indices (E/A, DTE, IVRT, LAVI) between BiA and RAA pacing groups. Additionally, these markers were within normal ranges. As there was no diastolic dysfunction in the studied population, raised mitral inflow can be primarily attributed to increased preload, resulting from optimal timing of LA contraction and its contribution to LV filling [13, 22].

Previous researchers defined the effects of altered preload on the indices of transmitral Doppler echocardiography [23–25].

Phasic function of LA may offer additional explanation of the results of our study. The LA mechanical function can be described by three phases within the cardiac cycle [26, 27]. Firstly, during ventricular systole and isovolumic relaxation, the LA functions as a “reservoir” that receives blood from pulmonary venous return and stores energy in the form of pressure. Secondly, during the early phase of ventricular diastole, the LA operates as a “conduit” for transfer of blood into the LV after mitral valve opening via pressure gradient. During LV diastasis, blood flows passively from the pulmonary veins into the LV. Thirdly, the “contractile” function of the LA normally serves to augment the LV stroke volume by approximately 20 % [28]. The relative contribution of this “booster pump” function becomes probably more dominant in the setting of BiA rather than RAA pacing as a result of synchronous, thus more effective LA contraction. These observations are convincing in the light of previous research, which suggested that the improvement of LA contractile function, expressed as LA ejection fraction, is possible after the reversion of atrial cardiomyopathy developed as a consequence of AF [29].

BiA in comparison to RAA pacing significantly shortened P wave duration and PQ interval. This observation confirms the results of previous studies. It is well established that RAA pacing impairs inter- and intra-atrial conduction and prolongs PQ interval; on the other hand, BiA pacing shortens it, in comparison to sinus rhythm [18, 20, 30, 31]. P wave shortening is obviously the result of simultaneous left and right atrial activations. PQ interval shortening might be the effect of quicker conduction from CS to A-V node in comparison to conduction from RAA to A-V node [16]. Additionally, the presence of two simultaneous depolarization wavefronts during BiA pacing increases the possibility of going round potential slow conduction areas in the atria [9, 32, 33].

In our study, BiA pacing turned out to be associated with lower serum ANP as well as lower proinflammatory hs-CRP, IL-6, and neopterin concentrations in comparison to RAA pacing. Both reduced ANP levels and PCWP indicate that mean atrial pressure and stretch are lower during BiA in comparison to RAA pacing. This might be due to more synchronous atrial contraction [18] and better A-V timing, which in this case is related to the increase of interval between the end of the atrial filling wave of transmitral flow and the mitral valve closure. This, in turn, prevents premature closure of the mitral valve before the completion of atrial contraction [34]. If A-V conduction is intact, the IAB during RAA pacing shortens the time available for LA activation, which is associated with premature mitral closure, abbreviated LA contraction, and therefore higher LA pressures and associated ANP levels. Lower atrial pressure and stretch during BiA pacing could partially explain its anti-arrhythmic effect [9, 35] since atrial stretch shortens the atrial refractory period, prolongs the

interatrial conduction time, and increases the dispersion of refractoriness [36].

Our study is the first to report that BiA in comparison to RAA pacing could be associated with the reduction of unfavorable prognostic proinflammatory markers of HF (hs-CRP, IL-6, and neopterin). A substantial body of evidence supports the concept that markers of inflammation (CRP and IL-6) are predictors of unfavorable cardiovascular events, including heart failure development [37–40] and all-cause mortality irrespective of cardiovascular disease [41, 42]. Moreover, elevated levels of proinflammatory markers such as IL-6 and CRP increase the risk of supraventricular and ventricular cardiac arrhythmias and their complications [43, 44].

One may, therefore, hypothesize that permanent BiA pacing, in comparison to RAA, might be associated with better prognosis. The National Health and Nutrition Examination Survey revealed significant correlation between P wave duration and increased cardiovascular and all-cause mortality [45]. In our study, P wave duration during BiA pacing was significantly shortened in comparison to RAA pacing, which seems consistent with changes in concentrations of proinflammatory markers. However, the issue requires further research to confirm whether this “anti-inflammatory” effect persists in longer observation.

4.1 Study limitations

The studied population is relatively small, and the variability of measured parameters is quite considerable. During the time, between pacemaker implantation and the experiment, patients were programmed to BiA pacing, which might have contributed to remodeling. We believe that even if a subtle remodeling occurred, it had no substantial effect on the study results. One should also be aware of the carry-over effect of the preceding pacing mode in the cross-over design during echocardiographic, hemodynamic and biochemical studies. We intended to lessen this effect by applying relatively long periods between measurements. For the cytokine assessment, each pacing mode was programmed for 7 days and therefore should not be extrapolated to represent the effect of chronic pacing. Five patients developed AF during RAA pacing, and those patients were excluded from the study to avoid effects of AF on atrial function, natriuretic peptides, and cytokines. If we assume that AF during RAA pacing was caused by escalated left A-V dyssynchrony, the exclusion of these patients might have diminished the studied effect. Different heart rates between subjects contributed to parameter variability and theoretically may have contributed to the differences in the findings. Finally, the influence of Doppler measurement reproducibility cannot be excluded. The reproducibility of Doppler measurements in our echo laboratory was 95 %, which we believe had no significant effect on the overall results of our study.

5 Conclusions

BiA pacing, in comparison to RAA pacing, acutely improves hemodynamic performance in patients with IAB and preserved A-V conduction and is associated with the reduction of ANP and markers of inflammation (hs-CRP, IL-6, and neopterin). Therefore, we provide an additional argument for considering BiA, instead of standard RAA pacing, which could improve cardiac hemodynamics and may influence prognosis in patients with IAB and preserved A-V conduction. Still, we believe that the results should be confirmed in a larger cohort of patients.

Conflict of interests None declared.

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